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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,448	ALPHEY, LUKE	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-27,29-35 and 43-48* is/are pending in the application.

4a) Of the above claim(s) *31,32 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-27,29,30,33-35,43,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/07/2009;10/04/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/25/2010 has been entered.

Claims 1-21, 23-27, 29-35, and 43-48 are pending. The amendment has been entered. Claims 22, 28, and 36-42 are canceled. Claims 31-32, 44-46 are withdrawn. Claims 1-21, 23-27, 29-30, 33-35, 43 and the newly added claims 47-48 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-4, 6-16, 18-21, 23-24, 29-30 and 43 under 35 U.S.C. 102(b) as being anticipated by Heinrich et al [PNAS, 97(15): 8229-8232, 2000 (IDS)] is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-16, 18-21, 23-24, 29-30, 43 under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Savakis et al** (US 2003/0150007); **Loukeris et al** (PNAS, 92: 9485-9489, 1995) is withdrawn in view of the amendment.

Claims 1-21, 23-27, 29-30, 33-35, 43 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Gossen et al** (Tetracycline in Biology, Chemistry and Medicine, pages 139-157, 2001); **Pane et al** (Development 129: 3715-3725 (2002); **Fussenegger et al** (Biotechnol Prog, 13: 733-740, 1997).

Heinrich et al teach a tetracycline-repressible female-specific lethal genetic system in the *Drosophila melanogaster* fly. The first component of the system is the tetracycline-controlled transactivator gene under the control of the fat body and female-specific transcription enhancer from the yolk protein 1 (yp1) gene. Heinrich teaches the first component system comprised of the *yp1-tTA* construct containing the female-specific transcription enhancer of the *yp1* gene inserted into the pBluescript II KS (−)vector. The fragment containing the *yp1* enhancer was inserted into the tTA transformation vector which is a CaspeR-derived vector into sites immediately upstream of the *hsp70* minimal promoter (first promoter) that is used to drive expression of the tTA coding sequence (p 8229, 2nd column, last paragraph bridge to p 8230, 1st column). The second component consists of the proapoptotic gene hid under the control of a

tetracycline-responsive element sequence (p 8229, 2nd column last paragraph bridge to p 8230 1st column). The construct *tetO-hid*, contains the complete *hid* ORF inserted into the *tetO* vector W.T.P.2 which is also a CaspeR-derived vector that contains seven copies of *tetO*, and a minimal promoter (second promoter) (p 8230, 1st column). Heinrich teaches the two component system with a positive control factor tTA which controls expression of both components by teaching expression of tTA is controlled by the female- and fat-body-specific enhancer from the *yp1* gene and binding of tTA to tetO results in activation of expression of the proapoptotic gene *hid* (p 8230, 1st column, under results, 4th paragraph) **(claims 1, 43).** Males and females of a strain carrying both components are viable on medium supplemented with tetracycline, but only males survive on normal medium (abstract) Heinrich teaches the expression of tTA is controlled with the female- and fat-body-specific transcription enhancer from the yp1 gene (figure 1) **(claim 2).** Heinrich teaches the yp1 enhancer is upstream of the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 2-4, 20-21, and 23**). Heinrich teaches in the absence of tetracycline, tTA binds to tetO and induced expression of the proapoptotic gene hid **(claim 6).** Heinrich teaches the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 7-9, 14).** Heinrich teaches the loss of fat body results in female-specific lethality (figure 1) and because ectopic expression of the proapoptotic gene hid can lead to transactivator (tTA), which is inactive in the presence of tetracycline expression of tTA is controlled with the female specific enhancer from the Drosophila yolk protein 1 (yp1) gene **(claims 10-12).** Heinrich teaches because the components of the system are either conserved (yolk protein genes) or known to function in both Drosophila and mammalian cells, the system could be used to make genetic-sexing strains for a variety of insect pests that can be genetically engineered (p 8229, 2nd column, 1st paragraph) **(claims 13, 16, 18, 20-21, 23).** Heinrich

teaches the system was designed such that female flies would die in the absence of tetracycline because of widespread cell death in the fat body, expression of tTA is controlled by the female- and fat-body-specific enhancer from the yp1 gene, binding of tTA to tetO results in activation of expression of the proapoptotic gene hid and induction of apoptosis in fat body results in female-specific lethality, because the fat body is an important tissue for metabolism and food storage in **insects (claims 14-21, 23-24).** Heinrich teaches the amount of induced ectopic cell death is very sensitive to the level of ectopic *hid* expression, which in the female lethal system depends directly on the level of tTA expression (p 8231, 2nd column, last paragraph) **(claim 18).** Transgene expression is influenced by the local chromatin environment, and tTA expression is controlled by the *yp1* enhancer, which may explain why the efficiency of the system depends on the sites of integration of the constructs and the level of yeast in the diet and the position effects could be minimized by bracketing the *yp1-tTA* and *tetO-hid* constructs with insulator elements **(claims 29, 30).** Heinrich teaches the effect of diet on female lethality is consistent with previous studies that showed that the *yp1* fat body enhancer is responsive to diet, particularly yeast and it will be of interest to determine whether the diet response is mediated via either the sex-specific double-sex protein or the proteins that bind to the β-zip or w3 sites of the enhancer, because the binding sites for all three proteins are required for enhancer function *in vivo* (p 8231, 2nd column, last paragraph) **(claim 19).** Heinrich teaches genes involved in the diet response potentially could be identified by carrying out sensitive genetic screens for mutations that either enhance female lethality on a low-yeast diet or suppress lethality on a high-yeast diet (p 8231, 2nd column, last paragraph).

However, Heinrich do not specifically teach wherein an expression product of the control factor gene of the first element to be expressed serves as a positive transcriptional control factor for both; (i) the at least one first promoter in said first element; and (ii) the at least one second

promoter in said second element. However, at the time of the instant invention **Gossen et al** (Tetracycline in Biology, Chemistry and Medicine, pages 139-157, 2001) teaches tTA and rtTA induce unwanted pleiotropic effects by "squelching" that may kill a cell (p 145, 4th paragraph). Gossen teaches the concentration of the tetracycline controlled transactivator should not exceed a certain intracellular concentration in cell cultures as well as in transgenic animals (p 145, 4th paragraph). Gossen suggests in order to overcome the squelching process is the creation of autoregulatory loops, where the transactivator not only controls the expression of the gene of interest, but also its own synthesis, i.e., the transactivator gene is under the promoter tetracycline (P_{tet}-1) control (p 146, 2nd paragraph). Gossen teaches the In *Drosophila melanogster* a highly efficient binary expression system is available, by which upon mating of individual transgenic flies, heterologous gene expression can be directed to specific tissues of the fly (p 151, last paragraph bridge to p 152). Gossen teaches this system is based on the transgenic expression of yeast Gal4 transcription factor and its binding site containing response promoters (p 151, last paragraph bridge to p 152). By driving expression of Gal4 via appropriate developmentally regulated promotes, the timing of expression can be controlled to a certain extent. However, the precise exogenous control as provided by the Tet system is not possible. Therefore, the adaptation of the Tet system to *Drosophila* offers new prospects for analyzing gene functions in this important model organism. Gossen teaches the Tet systern has actually been used to generate conditional male-only transgenic *Drosophila* lines by referring to the above tTA systems of Heinrich et al [PNAS, 97(15): 8229-8232, 2000 (IDS)]). Gossen teaches this approach might break ground in establishing a new and convenient method to obtain large, exclusively male populations of other insect species to be used in sterile insect release programs (p 152, 1st paragraph). Gossen teaches the construction of bidirectional promoters (P_{tet}-bi) where the heptamerized tetO sequences are flanked on both

sides by minimal promoters allows simultaneous regulation of two genes of interest, whereby the respective transcription units face in opposite directions and where one of the gene is a lacZ or GFP for allowing monitoring of the activity of the expression unit in situ (p 146, 2nd paragraph). Gossen et al teach when both the transactivator gene as well as the response unit are incorporated in a single vector on the other hand, there might be a significant interference between the transactivator driving promoter and (P_{tet}-1), potentially resulting in a less stringent regulation however, strategies like the cointroduction of silencer proteins or the design of properly "insulated" response units might alleviate this problem (p 144) **(claims 29-30** of the instant invention). **Pane et al** (Development 129: 3715-3725 (2002) teach codon usage in the Tet system where for example, in adult flies the transformer gene in Ceratitis capitata provides a genetic basis for selecting and remembering the sexual fate (title) **(claim 5** of the instant invention). Pane teaches that the female-specific transcript has a long open reading frame, while the male-specific mRNAs contain stop codons that abort prematurely the protein translation. Indeed partially different intronic sequences are retained in the M1 and M2 cDNA clones, adding stop codons in different positions (Fig. 2A). Pane suggests that a functional full-length TRA is only encoded by the female-specific transcripts. **Fussenegger et al** (Biotechnol Prog, 13: 733-740, 1997) teaches constructs where constructed di-, tri-, and quattrocistronic mammalian expression vectors which allow the simultaneous, coordinated, and adjustable expression of up to two product genes (abstract). A single, tetracycline-regulatable promoter, P_{hCMV}-1, drives high-level expression of a multicistronic expression unit, containing the product gene(s), the gene for tetracycline responsive transactivator (tTA) (abstract). This autoregulatory genetic configuration retains a very low basal transcription activity in the presence of tetracycline, thereby reducing or eliminating possible toxic effects of tTA expression (abstract). Fussenegger teaches these multicistronic, positive feedback regulation vectors to function in a

wide variety of eucaryotic cells and other vectors based upon the same autoregulation and multicistronic expression concepts can be constructed using other regulator gene-regulated promoter elements (abstract).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Gossen/Fussenegger to utilizing a multicistronic vector system as taught by Fussenegger to incorpotrate the Tet vector system as taught by Gossen in insect with a reasonable expectation of success. One of ordinary skill in art would have been motivated to introduce the Tet system of Heinrich into a multicistronic vector into a multicistronic vector in

order to drive expression of Gal4 via appropriate developmentally regulated promoters, to control timing of expression for analyzing sex specific and developmentally stage specific gene functions during insect development since Gossen teaches the Tet system has actually been used to generate conditional male-only transgenic *Drosophila* lines by referring to the above tTA systems of Heinrich et al [PNAS, 97(15): 8229-8232, 2000 (IDS)]). Gossen teaches heterologous gene expression directed to specific tissues of the fly via the tetracycline regulated gene expression might break ground in establishing a new and convenient method to obtain large, exclusively male populations of other insect species to be used in sterile insect release programs (p 152, 1st paragraph). This is further underscored by the teachings of Gossen that the construction of bidirectional promoters (P_{tet}-bi) where the heptamerized tetO sequences are flanked on both sides by minimal promoters allows simultaneous regulation of two genes of interest, whereby the respective transcription units face in opposite directions and where one of the gene is a lacZ or GFP for allowing monitoring of the activity of the expression unit in situ (p 146, 2nd paragraph).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants argue that Heinrich does not teach the salient and unique features of the present invention which employs positive feedback to control gene expression.

These arguments are not convincing because based on the amendment Gossen and Fussenegger provides a positive feedback to control gene expression as discussed above.

The rejection of claims **1, 17, 25-27** under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Bessereau et al., 2000 (WO 00/073510 A1)**; **Savakis et al (EP0955364 A2); Horn et al** (Nature Biotechnology, 21: 64-70, 2003 (IDS) is withdrawn in view of the amendment.

The rejection of claims **33-35** rejected under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Horn et al** (Nature Biotechnology, 21: 64-70, 2003 (IDS)) and further in view of **Horn et al** (Dev Genes Evol, 210:623–629, 2000) is withdrawn in view of the amendment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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